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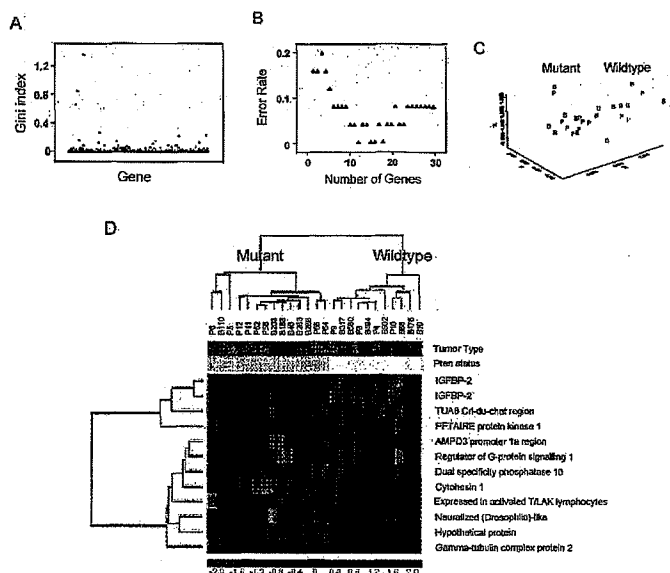
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— with international search report

[Continued on next page]

## (54) Title: MOLECULAR SIGNATURE OF THE PTEN TUMOR SUPPRESSOR



(57) Abstract: The present invention relates to the identification a molecular signature for PTEN tumor suppressor. The molecular signature comprising a gene or genes that are of use for diagnosis, prognosis, drug research and development and therapeutics. Specifically, the present invention relates to identification of IGFBP2 gene, its mRNA and/or protein products that closely associate with PTEN mutations. The present invention further demonstrates that IGFBP2 expression is negatively regulated by PTEN, positively regulated by PI3K and Akt activation, that IGFBP2 plays a functional role in the PTEN signaling and is required for Akt transformation. The use of IGFBP2 gene, its gene product such as its RNA transcript, protein and molecular probes in diagnosis, prognosis, drug discovery and validation and therapeutic target and therapeutics is also contemplated.



— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

**(88) Date of publication of the international search report:**  
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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/42258

## A. CLASSIFICATION OF SUBJECT MATTER

IPC: C12Q 1/68( 2006.01)  
C07H 21/02( 2006.01)

USPC: 435/6

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6, 91.1, 91.2, 183; 436/94; 536/23.1, 24.3, 24.33, 25.3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
Please See Continuation Sheet

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	US 2006/0127902 A1 (MADDEN et al) 15 June 2006 (15.06.2006), see whole document, especially see [0008] in pages 4 -6 and claim 22 in pages 159-161	claims 1-20

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/42258

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:  
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-20

- Remark on Protest**
- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
  - ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
  - ☐ No protest accompanied the payment of additional search fees.

**BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING**

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-20, drawn to a method of profiling a tumor/cancer in human tissue specimens wherein said gene is insulin-like growth factor binding protein 2.

Group II, claims 21-43, drawn to a method of screening a compound inhibits cancer cell growth.

Group III, claims 44-58, drawn to an assay kit of profiling a tumor/cancer in human tissue specimens.

Group IV, claims 59 and 60, drawn to a therapeutic useful antibody against insulin-like growth factor binding protein 2 or IGFBP2.

Note that, since claims 8 and 9 has a lot of genes which have different structures and different functions, Group I is divided to many different subgroups each subgroup has different genes, applicant requires to select a single gene for the examination. Applicant is advised that examination will be restricted to only elected gene and should not to be construed as a species election.

The inventions listed as Groups I to IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because they lack the same or corresponding special technical features. For example, profiling a tumor/cancer in human tissue specimens in claim 1 of Group I is not required for Group II while screening a compound that inhibits cancer cell growth in claim 21 of Group II is not required for Group I.

Groups I and III do not relate to a single general inventive concept under PCT Rule 13.1 because the technical feature linking Groups I and III is not special. For example, an assay kit of Group III is not a contribution over the prior art since a kit containing antibodies against HC gp-39 in US Patent No. 5,726,06 (published on March 10, 1998) reads an assay kit of Group III.

Groups I and IV do not relate to a single general inventive concept under PCT Rule 13.1 because the technical feature linking Groups I and III is not special. For example, profiling a tumor/cancer in human tissue specimens in claim 1 of Group I is not required for Group IV while a therapeutic useful antibody against insulin-like growth factor binding protein 2 in claim 59 of Group IV is not required for Group I.

Groups II and III do not relate to a single general inventive concept under PCT Rule 13.1 because the technical feature linking Groups II and III is not special. For example, an assay kit of Group III is not a contribution over the prior art since a kit containing antibodies against HC gp-39 in US Patent No. 5,726,06 (published on March 10, 1998) reads an assay kit of Group III.

Groups II and IV do not relate to a single general inventive concept under PCT Rule 13.1 because they lack the same or corresponding special technical features. For example, screening a compound that inhibits cancer cell growth in claim 21 of Group II is not required for Group IV while a therapeutic useful antibody against insulin-like growth factor binding protein 2 in claim 59 of Group IV is not required for Group II.

Groups III and IV do not relate to a single general inventive concept under PCT Rule 13.1 because they lack the same or corresponding special technical features. For example, an assay kit in claim 44 of Group III is not required for Group IV while a therapeutic useful antibody against insulin-like growth factor binding protein 2 in claim 59 of Group IV is not required for Group III.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US04/42258

Continuation of B. FIELDS SEARCHED Item 3:

STN and EAST

Search terms: cancer or tumor, express\$, gene, human, compound or reagent or substance, and insulin-like growth factor binding protein